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A Phase 2, Open-Label Study to Evaluate the Safety and Efficacy of the Probody® Therapeutic (Pb-Tx) Praluzatamab Ravtansine (CX-2009) in Metastatic HR-Positive/HER2-Negative Breast Cancer (mHR+/HER2− BC) and of CX-2009 as Monotherapy and in Combination Therapy With Pacmilimab (CX-072) in Metastatic Triple-Negative Breast Cancer (TNBC)

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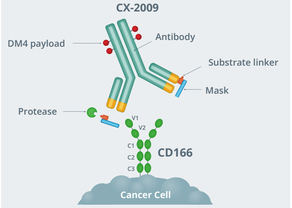
BACKGROUND

- Probody drug conjugates are a new class of recombinant proteolytically activated antibody prodrugs consisting of 4 molecular components: the antibody; a peptide masking the antigen-binding site of the antibody; a protease cleavable linker designed to keep the peptide mask in place; and a toxin conjugated to the antibody (**Figure 1**)[1]

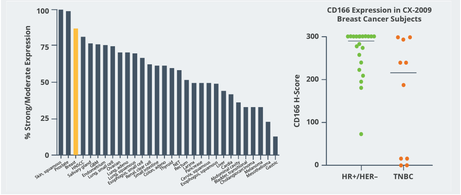
Figure 1. CX-2009: a Probody drug conjugate targeting CD166.



- Upregulated tumor protease activity, a hallmark of cancer, cleaves the substrate linker and releases the masking peptide, which allows the antibody to bind to its target[2]

- CX-2009 is a Probody drug conjugate that consists of a humanized anti-CD166 monoclonal antibody conjugated to DM4, a potent microtubule inhibitor known to be active against multiple cancer types (**Figure 1**)
  - CD166 (activated leukocyte cell adhesion molecule) is a transmembrane protein that functions as a junctional adhesion molecule and facilitates cell migration, differentiation, and hematopoiesis. It is widely expressed on dividing, normal, and malignant cells (**Figure 2**)[3]
  - The incidence of high CD166 expression is >80% for ER+/HER2– breast cancer and ~50% for triple-negative breast cancer (TNBC) (**Figure 2**)
  - As designed, CX-2009 should restrict target engagement to tumors that express CD166. Off-tumor/on-target toxicity should be reduced; non-specific payload toxicity should be similar to that of other DM4 antibody-drug conjugates (ADCs)

Figure 2. CD166 expression among different tumor types.



Summary

- Probody technology enables administration of an ADC against a previously undruggable ADC target at tolerable doses with signs of clinical benefit

Rationale to Combine with Immune Checkpoint Inhibitors

- Cytotoxic payloads not only have cytotoxic effects but may also potentiate an immune response through multiples modalities
  - Cytotoxic payload/ADCs have been shown to induce immunogenic cell death in vitro and in vivo[4]
  - Immunologic cell death is described as the release of danger signals or damage-associated molecular patterns that elevate the immunogenic potential of dying cells[5]
  - In addition to elevating the immunogenic potential of cancer cells, cytotoxic payloads can also provoke phenotypic and functional dendritic cell maturation and activation[6]
  - Data available from 2 clinical studies of maytansinoid-based ADCs in combination with immune checkpoint inhibitors support the benefit of these combinations in patients[7,8]

CTMX-M-2009-001 Study

- Dose escalation/dose-expansion trial (n=99)
- 27 sites in US, Spain, Netherlands, and UK
- Advanced, pretreated solid tumors with disease progression after standard treatments
- Available tumor tissue for CD166 IHC analysis
- Prior maytansinoid treatment and neuropathy > Grade 1 exclusionary
- Evaluated two schedules
  - Q3W: 0.25 mg/kg – 10 mg/kg (n=89)
  - Q2W: 4 mg/kg – 6 mg/kg (n=10)

Summary of CX-2009 Phase 1 Data

Clinical Activity

- Tumor volume regression observed at CX-2009 doses ≥4 mg/kg IV Q3W
- Confirmed partial responses and clinically meaningful disease control, as measured by CBR16 (39%) and CBR24 (27%) was observed in patients with breast cancer

Clinical Safety

- Adverse events at the recommended phase 2 dose of 7 mg/kg Q3W are manageable
  - Ocular toxicity is dose related with higher incidence at doses ≥8 mg/kg Q3W
  - Most events recover/resolve within 2-3 weeks with either treatment interruption or ocular medications
- Ocular prophylaxis required: ophthalmic vasoconstricting agents, corticosteroids, and artificial tears
- Based on activity and tolerability, the RP2D is 7 mg/kg Q3W

Translational Findings (See Liu, et al. SABCS 2020 PS11-07)

- CX-2009 is activated/unmasked in tumors and is predominantly intact/masked in circulation
- Correlations between activated CX-2009 and CD166 levels suggest a role for target expression in the unmasking and/or tumor retention of CX-2009
- CD166 expression could be beneficial for selection of patients

OBJECTIVES

Arms A and B (CX-2009 Monotherapy)

Primary

- To evaluate the antitumor activity of CX-2009 based on objective response rate (ORR) per Central Radiology Review (CRR)

Secondary

- To evaluate the antitumor activity of CX-2009 based on ORR per Investigator assessment
- To evaluate progression-free survival (PFS), clinical benefit rate at 16 weeks (CBR16), clinical benefit rate at 24 weeks (CBR24), duration of response (DoR), and overall survival (OS)
- To characterize the safety profile of CX-2009
- To characterize the PK of CX-2009
- To assess the incidence of antidrug antibody (ADA) formation to CX-2009

Arm C (CX-2009 + CX-072 Combination Therapy)

Primary

- To evaluate the antitumor activity of CX-2009 in combination with CX-072, a protease activatable IgG4 mAb prodrug to PD-L1, based on ORR per CRR

Secondary

- To evaluate the antitumor activity of CX-2009 in combination with CX-072 based on ORR per Investigator assessment
- To evaluate PFS, CBR16, CBR24, DoR, and OS
- To characterize the safety profile of CX-2009 in combination with CX-072
- To characterize the PK and assess the incidence of ADA formation with the combination of CX-2009 and CX-072

STATISTICAL METHODS

- The primary endpoint will be ORR according to RECIST v1.1 based on assessment by the CRR
  - Analyses will be performed separately for each arm using the modified efficacy-evaluable population, defined as all patients who have at least 1 post-baseline tumor scan centrally assessed by the CRR

Analysis of the Secondary Efficacy Endpoints

- The analyses specified for the primary efficacy endpoint will be repeated for Investigator-assessed ORR (as supportive measure of evidence)
- Estimates of clinical benefit rate (CBR16 and CBR24) will be determined for assessments made by both the CRR and the Investigator. DoR will also be summarized using descriptive statistics (eg, median and range) for both CRR- and Investigator-assessed responses
- Analyses of other secondary efficacy variables will be performed for each arm in the safety-evaluable population, defined as all patients who received at least 1 dose of study drug regardless of the duration of treatment
- PFS and OS will be summarized using Kaplan-Meier product-limit methods, including estimates of median PFS and OS, and estimates of PFS and OS survivor functions at specific timepoints (eg, 6 months) with their associated 95% CIs

STUDY DESIGN

Phase 2, prospective, open-label, parallel-cohort, multicenter, 3 arm interventional study of CX-2009 monotherapy or in combination with CX-072 in patients with advanced breast cancer (NCT04596150)

Inclusion:
- ECOG PS 0 or 1
- Adequate hematologic, renal, and hepatic function
- Measurable disease
- Available tumor tissue (archival or fresh biopsy) for CD166 analysis

Exclusion:
- Untreated symptomatic CNS metastases
- Prior malignancy with in past 2 years unless considered low risk for recurrence
- Prior maytansinoid-containing drug conjugate treatment

Arm C: history of intolerance to prior I/O treatment

Arm A
CX-2009 (7 mg/kg) Q3W
HR+/HER2- (N=40)

Arm B
CX-2009 (7 mg/kg) Q3W
TNBC (N=40)

Arm C
CX-2009 (7 mg/kg) +
CX-072 (1200 mg) Q3W
TNBC (N=40)

Endpoints

Primary: ORR by Central Radiology Review

Secondary: ORR (inv), PFS, DCR, CBR24, DoR, OS, safety, PK, ADA

Exploratory: Biomarker correlation with outcome

Status

The study is open for enrollment

ELIGIBILITY CRITERIA

Inclusion Criteria

All Patients

1. Adults ≥18 years of age with adequate organ function and measurable inoperable, locally advanced, or metastatic breast cancer

HR+/HER2 Negative Eligibility

2. Histologically confirmed HR-positive/HER2-negative breast cancer based on the most recent analyzed biopsy defined as
   a. ER/PgR >10% (patients with ER/PgR < 10% by IHC should be enrolled in the TNBC cohort(s) unless otherwise agreed). NOTE: The biopsy for ER/PgR receptor status confirmation should be taken from metastatic disease, the pathology data for ER/PgR receptor expression should be taken from the primary tumor
   b. HER2 negative: IHC 0 or 1+ or HER2/CEP17 ratio 2.0 and average HER2 copy number <4.0 signals/cell) by ISH
3. 0 to 2 prior cytotoxic chemotherapy for advanced disease. Prior lines of therapy must meet the following criteria:
   a. There is no limit to the number of anti-cancer hormonal monotherapy or doublet regimens; the number of prior hormone-based treatments will not count toward the prior treatment requirements for eligibility
   b. At least 1 CDK4/6 inhibitor in any treatment setting is required
4. Patients with brain metastases that are ≤ 1 cm, are asymptomatic, and require treatment may be eligible after discussion with medical monitor. Patients with central nervous system lesions that are equivocal (ie, may or may not be brain metastases) as assessed by the Investigator may be enrolled without definitive local treatment

TNBC Eligibility

1. Histologically confirmed TNBC based on the most recent analyzed biopsy
2. Tumor tissue must have high CD166 expression by IHC
3. Received at least 1 but no more than 3 prior systemic lines of treatment regimens for advanced disease
4. Received a taxane-based regimen in any setting
5. Patients with known germline *BRCA 1/2* mutations must have received a platinum or PARP inhibitor.
6. Tumor tissue known to be PD-L1 positive (Part C only)

Exclusion Criteria

1. History of malignancy that is active within the previous 2 years except for localized cancers that are not related to the current cancer being treated that are considered to have been cured, and present a low risk for recurrence
2. Prior maytansinoid-containing drug conjugates (ie, trastuzumab emtansine)
3. Untreated, symptomatic brain, and/or leptomeningeal metastases
4. Unresolved Grade >1 toxicity from prior treatment (alopecia and non-acute toxicities excepted)
5. Active or chronic corneal disorders
6. Active viral hepatitis, CMV, or HIV infection
7. Significant cardiac disease
8. History of MS, or other demyelinating diseases, Eaton-Lambert syndrome, hemorrhagic or ischemic stroke within 6 months of enrollment, or alcoholic liver disease
9. Prior allogeneic solid organ, stem cell, or bone marrow transplant

Arm C only

1. History of intolerance to prior immune CPI therapy defined as a requirement by local practice guidelines to discontinue treatment due to an immune-related adverse event
2. History of or current active autoimmune diseases, which are not a sequelae of prior immune checkpoint therapy
3. Myocarditis
4. History of intolerance to prior checkpoint inhibition
5. Immunosuppressive therapy within 14 days of C1D1 (ie, ≥10 mg daily prednisone or equivalents)
6. Progressed within 120 days of the first dose of the checkpoint inhibitor

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